

**HEART FAILURE UPDATE**

# Eplerenone Survival Benefits in Heart Failure Patients Post-Myocardial Infarction

Efsthathia Prappa, MD

**ABSTRACT**

Reduced left ventricular ejection fraction ( $\leq 40\%$ ) and/or signs of clinical heart failure after acute myocardial infarction (AMI) are associated with a relatively high incidence of mortality and hospitalization for heart failure. The potential of eplerenone to impact on mortality and morbidity of post-infarction heart failure patients was the subject of the EPHEUS trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study). That trial concluded that eplerenone reduced total mortality by 31%, cardiovascular mortality by 32% and sudden cardiac death by 37% within 30 days of randomization after AMI. Risk reduction in mortality with eplerenone seemed to occur as early as 10 days after randomization and continued through the end of the study. In conclusion, eplerenone improves survival in heart failure patients post-AMI.

*2<sup>nd</sup> Cardiology Department,  
Evangelismos General Hospital, Athens,  
Greece*

**KEY WORDS:** *eplerenone; heart failure; acute myocardial infarction; aldosterone antagonists*

Reduced left ventricular ejection fraction (LVEF) ( $\leq 40\%$ ) and/or signs of clinical heart failure after acute myocardial infarction (AMI) are associated with a relatively high incidence of mortality and hospitalization for heart failure.<sup>1</sup> Of importance, patients with signs of heart failure post-infarction have a three- to four-fold increased risk of in-hospital death and a 55% increased risk of dying within 30 days after AMI in comparison with patients with an acute infarction but no signs of heart failure.<sup>1,2</sup> This early increase in risk in patients with a reduced LVEF and clinical signs of heart failure argues for therapeutic interventions as early as possible after AMI.

It is already well established that aldosterone blockade reduces the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes, among patients with severe heart failure due to left ventricular systolic dysfunction.<sup>3</sup> Aldosterone blockade also prevents ventricular remodeling and collagen formation in patients with left ventricular systolic dysfunction after AMI.

Eplerenone is an aldosterone blocker that selectively blocks the mineralocorticoid receptor and not the glucocorticoid, progesterone or androgen receptors. The potential of eplerenone to impact mortality and morbidity of post-infarction heart failure patients was the subject of the EPHEUS trial (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study). That multicenter, double-blind, randomized, international trial included 6,632 patients with AMI complicated by left

**ABBREVIATIONS**

AMI = acute myocardial infarction

LVEF = left ventricular ejection fraction

*Correspondence to:*

Efsthathia Prappa, MD, Evangelismos  
Hospital, Athens, Greece; E-mail:  
[efiprappa@gmail.com](mailto:efiprappa@gmail.com)

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ventricular dysfunction (LVEF  $\leq 40\%$  by echocardiogram, radionuclide angiography, or left ventricular angiography) and clinical signs of heart failure (i.e., the presence of pulmonary rales, pulmonary venous congestion on chest radiograph, or the presence of a third heart sound). The clinical evidence of heart failure could be transient, occurring at any time from the onset of the index AMI, and did not necessarily need to be present at the time of randomization. Post-AMI patients with diabetes mellitus were only required to have an LVEF  $\leq 40\%$ . Eligible patients were randomized between 3 and 14 days after AMI to treatment with eplerenone in addition to standard medical therapy. Patients with a serum potassium concentration  $>5.0$  mmol/l or a serum creatinine concentration  $>2.5$  mg/dl were excluded. The two primary end points were time to death from any cause and time to death from cardiovascular causes or first hospitalization for a cardiovascular event (heart failure, recurrent AMI, stroke or ventricular arrhythmia). The major secondary end points were death from cardiovascular causes and death from any cause or any hospitalization.

Finally, it was shown that eplerenone at a dose of 25 mg/day, reduced total mortality by 31%, cardiovascular mortality by 32% and sudden cardiac death by 37% within 30 days of randomization after AMI. Risk reduction in mortality with eplerenone seemed to occur as early as 10 days after randomization and continued through the end of the study (the mean duration of follow-up was 16 months).<sup>4,5</sup>

The mechanisms by which eplerenone provides myocardial protection in patients with AMI complicated by left ventricular dysfunction and heart failure are not completely clear. Effects of aldosterone blockers on plasma volume and electrolyte excretion have been recognized for many years, and although these effects may have contributed to the benefit provided by eplerenone, other nonrenal mechanisms may be equally or more important. Eplerenone reduces coronary vascular inflammation and the risk of subsequent development of interstitial fibrosis, reduces oxidative stress,<sup>6</sup> improves endothelial dysfunction, attenuates platelet aggregation, decreases activation of matrix metalloproteinases and improves ventricular remodeling.<sup>7</sup>

In conclusion, eplerenone survival benefits are crystal clear in heart failure patients post-AMI. In the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008<sup>8</sup>, the following class I recommendation (level of evidence B) is put forth for aldosterone antagonists: "Unless contraindicated or not tolerated, the addition of a low-dose of an aldosterone antagonist should

be considered in all patients with an LVEF  $\leq 35\%$  and severe symptomatic heart failure, i.e. currently New York heart Association (NYHA) functional class III-IV, in the absence of hyperkalemia and significant renal dysfunction. Aldosterone antagonists reduce hospital admission for worsening heart failure and increase survival when added to existing therapy, including an angiotensin converting enzyme inhibitor. In hospitalized patients satisfying these criteria, treatment with an aldosterone antagonist should be initiated before discharge".

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